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Association between birth weight and visceral fat in adults¹⁻³

Emanuella De Lucia Rolfe, Ruth JF Loos, Céline Druet, Ronald P Stolk, Ulf Ekelund, Simon J Griffin, Nita G Forouhi, Nicholas J Wareham, and Ken K Ong

ABSTRACT

Background: Several studies reported inverse associations between birth weight and central adiposity in adults. However, few studies investigated the contributions of different abdominal fat compartments.

Objective: We examined associations between birth weight and adult visceral and subcutaneous abdominal fat in the population-based Fenland study.

Design: A total of 1092 adults (437 men and 655 women) aged 30–55 y had available data on reported birth weight, standard anthropometric measures, and visceral and subcutaneous abdominal fat estimated by ultrasound. In a subgroup ($n = 766$), dual-energy X-ray absorptiometry assessment of total abdominal fat was performed. Linear regression models were used to analyze relations between birth weight and the various fat variables adjusted for sex, age, education, smoking, and body mass index (BMI).

Results: After adjustment for adult BMI, there was an inverse association between birth weight and total abdominal fat [B (partial regression coefficient expressed as SD/1-kg change in birth weight) = -0.09 , $P = 0.002$] and visceral fat ($B = -0.07$, $P = 0.01$) but not between birth weight and subcutaneous abdominal fat ($B = -0.01$, $P = 0.3$). Tests for interaction showed that adult BMI modified the association between birth weight and visceral fat (P for interaction = 0.01). In stratified analysis, the association between birth weight and visceral fat was apparent only in individuals with the highest BMI tertile ($B = -0.08$, $P = 0.04$).

Conclusions: The inverse association between birth weight and adult abdominal fat appeared to be specific to visceral fat. However, associations with birth weight were apparent only after adjustment for adult BMI. Therefore, we suggest that rapid postnatal weight gain, rather than birth weight alone, leads to increased visceral fat. *Am J Clin Nutr* 2010;92:347–52.

INTRODUCTION

Obesity has become a major worldwide public health issue, and its prevalence has increased drastically over the last 30 y in all age groups (1–3). The increased availability and consumption of foods of high-energy density combined with a more sedentary lifestyle have probably contributed to this rapid rise (2). However, early life factors, both prenatal and postnatal, may play a significant role in the development of obesity and its related comorbidities such as type 2 diabetes and cardiovascular disease (4–11). Studies in animal models have shown that the metabolism of adipose, lean, and hepatic tissues may be programmed by maternal nutrition during gestation and lactation (12, 13). In particular, animals that experienced a combination of early

growth restraint and subsequent overnutrition presented features of insulin-resistance syndrome (12). However, the relevant mechanisms in humans are unclear, and the associations with birth weight (BW) have been inconsistent.

A link between early life factors and the distribution and quantity of visceral and subcutaneous fat could lead to altered risks for obesity-related metabolic diseases in adult life. Several studies have reported an inverse association between BW and abdominal or truncal adiposity in children and adults (5, 14–18). However, other studies have shown a U-shape relation between BW and abdominal adiposity (8, 17, 19). These inconsistencies may be partly explained by the variety of methods used to assess abdominal adiposity. Most of these epidemiologic studies relied on estimates of total abdominal fat, such as waist circumference, waist-hip ratio, skinfold thickness, and dual-energy X-ray absorptiometry (DXA), whereas very few studies investigated the contributions of the specific visceral or subcutaneous abdominal fat compartments (20). More precise measures of these fat tissues may help elucidate the relation between BW, fat distribution, and subsequent obesity because visceral and subcutaneous fat have very different metabolic consequences (21). Increased visceral fat is related to insulin resistance, whereas subcutaneous adiposity is more strongly associated with circulating leptin concentrations and generalized obesity (22). The use of reference imaging techniques such as magnetic resonance imaging (MRI) and computed tomography is restricted in large-scale population studies because of ethical and practical issues (21). Ultrasonography is a valid epidemiologic tool for estimating specific abdominal fat depots when MRI and computed tomography are not feasible (21). Therefore, we examined the relations between BW and adult visceral and subcutaneous abdominal fat by using ultrasonography in a large-scale population-based study. We hypothesized that BW might have differential associations with adult visceral and subcutaneous abdominal fat.

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SUBJECTS AND METHODS

Study population

The Fenland study is a population-based cohort study that uses objective measures of disease exposure, such as accurate methods of body composition and energy expenditure, to study the interactions between genetic and lifestyle factors that cause obesity and diabetes. The volunteers are recruited from general practice lists in and around Cambridgeshire (Cambridge, Ely, and Wisbech) in the United Kingdom from birth cohorts from 1950–1975. Recruitment started in 2004 and it is still active. The study will eventually include 10,000 individuals aged 30–55 y.

Of the initial 1500 healthy adult volunteers (aged 30–55 y) in this study, in the current analyses we included 1092 individuals (437 men and 655 women) who had complete information on BW and a BW ≥ 1.5 and ≤ 5.0 kg to avoid extreme outliers (excluded individuals: $n = 11$ with a BW < 1.5 kg and $n = 6$ with a BW > 5.0 kg). No significant differences were shown between participants included and excluded in current anthropometric and body composition variables (data not shown).

Participants attended the Medical Research Council Epidemiology Unit Clinical Research Facilities, Princess of Wales Hospital, Ely, United Kingdom; the North Cambridgeshire Hospital, Wisbech, United Kingdom; or the Institute of Metabolic Science, Cambridge, United Kingdom between January 2005 and October 2007. Exclusion criteria of the Fenland study included pregnancy, diabetes, an inability to walk unaided, psychosis, or terminal illness. The study was approved by the Cambridge Local Research Ethics Committee and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

Study measures

Anthropometric measures

Participants were measured barefoot and wore light clothing. Weight was measured to the nearest 200 g with a calibrated electronic scale (TANITA model BC-418 MA; Tanita, Tokyo, Japan). Height was assessed to the nearest 0.1 cm with a wall-mounted stadiometer (SECA 240; Seca, Birmingham, United Kingdom). Body mass index (BMI; in kg/m^2) was calculated as weight divided by square height. Waist circumference and hip circumference were measured to the nearest 0.1 cm with a nonstretchable fiber-glass insertion tape (D loop tape; Chasmors Ltd, London, United Kingdom). Waist circumference was defined as the midpoint between the lowest rib margin and the iliac crest, and hip circumference was defined as the widest level over the trochanters. All measurements were taken by trained field workers. Birth weight was based on self-report. Volunteers were requested to find out their BW before their visit.

Body composition

The body composition of each individual was assessed by using DXA and ultrasonography. Volunteers were instructed to refrain from eating 10 h before their arrival at the research facility because of the glucose tolerance test undertaken for the main study and to decrease bowel peristalsis for the ultrasound procedure.

DXA

DXA measurements were conducted with a Lunar Prodigy Advanced fan beam scanner (GE Healthcare, Bedford, United Kingdom) with a constant pixel size of 1.2×1.2 mm. Estimates of total body fat mass and total abdominal fat (g) were derived with Prodigy enCORE software (version 10.51.006; GE Healthcare). The DXA abdominal fat region (g) was defined by quadrilateral boxes with the base of the box touching the pelvis and the lateral boundaries extending to the edge of the abdominal soft tissue. Before the scan, participants were asked to remove any metal objects, such as jewelry, that could attenuate the X-ray beam. Participants were positioned on the DXA table according to the protocol recommended by the supplier, in which the subject laid supine and motionless with arms at their side. Before the scanning session, the equipment was calibrated according to the standard procedures supplied by the manufacturer. The CV for scanning precision, calculated from 30 consecutive scans of an external luciate and high-density polyethylene hologic phantom, was 2.0% for total fat mass. The effective radiation dose in each examination was 0.08 microsieverts (μSv).

Ultrasonography

A LOGIQ Book XP ultrasound system (USS) (GE Healthcare) with a 3C-RS curved transducer was used to determine visceral and subcutaneous abdominal fat thicknesses. USS visceral fat thickness was defined as the depth (cm) from the peritoneum to the lumbar spine, and USS subcutaneous abdominal fat was defined as the depth (cm) from the skin to the linea alba (23). Both measurements were obtained from where the xyphoid line and the waist circumference met. Measurements were made at the end of a quiet expiration by applying minimal pressure to ensure no displacement of the abdominal cavity. The relative intraobserver technical error of measurement (TEM) for the visceral thickness ranged between 1.8–2.9% and 0.6–3.0% for subcutaneous fat thickness, whereas the relative interobserver technical error of measurement was 2.4% for visceral thickness and 2.1% for subcutaneous thickness.

Other covariates

Information on the educational level and smoking status of subjects was collected by using a health and lifestyle questionnaire. Educational level was categorized as follows: 1) no formal qualifications, 2) low (primary school: School Leaving Certificate, Certificate of Secondary Education, or Ordinary Level), 3) moderate (high school: City & Guilds qualifications, apprenticeship, matriculation, trade, or Advanced Level), and 4) high (higher vocational, college, or university education). Smoking status was classified into 3 categories as follows: 1) never smoked, 2) former smoker, and 3) current smoker.

Statistical analyses

Statistical analyses were performed with STATA (version 9.2; StataCorp, College Station, TX). Results are presented as means (\pm SD) or n (%). Unpaired t and chi-square tests were used to compare population characteristics by sex. Relations between adiposity variables were assessed by Pearson's correlation.

Regression models were derived to analyze the relations between BW (exposure) and the various body fat variables (outcomes). To test the assumption of linearity, the quadratic term for BW was added to the models. Because this was not significant, the linear models were pursued instead. To examine whether the association between BW and the fat variables differed between sexes, the interaction term (sex \times BW) was added to the models. Because the associations did not differ by sex, we performed pooled analyses with adjustment for sex. A hierarchical and pragmatic approach was used to identify the effect of possible confounders on these relations. Two final models were constructed as follows: model A was adjusted for sex, age, educational level, and smoking status, and model B was further adjusted for BMI. The variance inflation factor was used to detect collinearity between the different variables when BMI was included to the models. If the variance inflation factor was >5 for any 2 covariates, only one covariate was included in the prediction model. Partial regression coefficients (B) were reported (SD/1-kg change in BW). A modification of the association between BW and visceral fat by BMI was tested by adding the interaction term (BW \times BMI) to the models. For ease of presentation, tertiles of BMI and BW were derived, and visceral fat was calculated, in 9 subgroups created according to these tertiles.

RESULTS

Population characteristics are summarized in **Table 1**. Men had greater BW, height, weight, BMI, total abdominal fat, and visceral fat but lower total body fat and subcutaneous abdominal fat than did women. The intercorrelations between adiposity variables are reported in **Table 2**. There was a relatively weak correlation between visceral fat and subcutaneous abdominal fat ($r = 0.30$). Subcutaneous fat was more strongly related to total body fat, whereas visceral fat was more strongly related to BMI, waist circumference, and total abdominal fat.

The results of the multiple linear regression models adjusted for sex, age, educational level, and smoking status are shown in **Table 3**. Birth weight was positively associated with adult BMI. Without adjustment for BMI (model A), BW was not associated with waist circumference or any measure of body composition. In contrast, with the additional adjustment for BMI (model B), BW was inversely associated with total abdominal fat and visceral fat.

Tests for interaction showed that the association between BW and visceral fat was modified by BMI (P for interaction = 0.01). In a stratified analysis by tertiles of BMI, the association between BW and visceral fat was strongest in individuals with the highest BMI tertile ($B = -0.08$, $P = 0.04$) but was not apparent in the 2 lower BMI tertiles (tertile 1: $B = -0.01$, $P = 0.7$; tertile 2: $B = -0.04$, $P = 0.15$) (**Figure 1**). The greatest mean visceral fat was observed in the group with the lowest BW tertile and the highest current BMI tertile.

DISCUSSION

In a large population-based study, we observed that BW was inversely associated with total abdominal fat estimated by DXA and with visceral fat but not subcutaneous abdominal fat estimated by ultrasound. This BW association with total abdominal

TABLE 1
Population characteristics

| Variables | Men (<i>n</i> = 437) | Women (<i>n</i> = 655) | <i>P</i> ¹ |
|--|-----------------------------|----------------------------|-----------------------|
| Age (y) | 43.7 \pm 7.2 ² | 44.3 \pm 7.2 | 0.18 |
| Birth weight (kg) | 3.5 \pm 0.5 | 3.3 \pm 0.5 | <0.0001 |
| Weight (kg) | 88.2 \pm 14.4 | 71.8 \pm 16.8 | <0.0001 |
| Height (cm) | 178.1 \pm 6.2 | 164.2 \pm 6.4 | <0.0001 |
| BMI (kg/m ²) | 27.8 \pm 4.2 | 26.7 \pm 6.0 | 0.0006 |
| Waist circumference (cm) | 99.3 \pm 12.0 | 86.9 \pm 13.4 | <0.0001 |
| Hip circumference (cm) | 106.0 \pm 7.6 | 104.0 \pm 12.3 | 0.02 |
| Waist-hip ratio | 0.94 \pm 0.1 | 0.83 \pm 0.1 | <0.0001 |
| Total body fat (g) ³ | 24,998 \pm 8105 | 26,861 \pm 10,894 | 0.01 |
| Total abdominal fat (g) ³ | 2816 \pm 1063 | 2290 \pm 1246 | <0.0001 |
| Visceral fat thickness (cm) ⁴ | 6.4 \pm 2.0 | 4.3 \pm 1.8 | <0.0001 |
| Subcutaneous abdominal fat thickness (cm) ⁴ | 2.8 \pm 1.0 | 3.2 \pm 1.3 | <0.0001 |
| Smoking status ⁵ [<i>n</i> (%)] | | | 0.4 ⁶ |
| Never | 175 (52.1) | 273 (54.4) | |
| Former | 104 (31.0) | 160 (32.0) | |
| Current | 57 (17.0) | 69 (13.8) | |
| Educational level [<i>n</i> (%)] ⁷ | | | 0.06 ⁶ |
| No qualifications | 27 (6.2) | 53 (8.2) | |
| Low | 73 (16.7) | 137 (21.1) | |
| Medium | 159 (36.5) | 195 (30) | |
| High | 177 (40.6) | 265 (40.7) | |

¹ Student's *t* test was used to compare anthropometric measures and body fat variables across sexes.

² Mean \pm SD (all such values).

³ Assessed by dual-energy X-ray absorptiometry; data were available for 766 individuals.

⁴ Assessed by ultrasound.

⁵ Data were available for 838 individuals.

⁶ Chi-square test was used for heterogeneity.

⁷ Data were available for 1086 individuals.

fat estimated by DXA is consistent with several previous studies (18, 24, 25). However, DXA does not distinguish between visceral and subcutaneous fat compartments. To our knowledge, this study is the first to use ultrasound-derived estimates of visceral and subcutaneous fat in relation to BW. Our findings indicate that the inverse association between BW and adult central adiposity seems to be specifically because of a relation with visceral fat rather than subcutaneous abdominal fat.

Previous studies that used MRI scans in newborns showed that newborns with low BW already have increased visceral fat at birth (22). However, in our study the associations with BW were only observed after adjustment for adult BMI. Adjustment for adult body size is a controversial topic when the relation between BW and adult health is analyzed. This adjustment might create a statistical artifact known as the reversal paradox, which occurs if the variable adult body size is in the causal pathway between BW and the health outcome investigated (26). Adjustment could potentially introduce bias because of inappropriate controlling (26). However, such adjustments have been justified where later a body size variable is a potential confounder, and it is positively related both to BW and to the outcome of interest (27–29). Furthermore, Lucas et al (27) and Cole (30) argued that any resulting change in association after adjustment for BMI is indicative of the importance of weight gain between birth and follow-up rather than BW itself. Therefore, the dependence of our association between BW and adult visceral fat after adjustment for adult BMI could support the

TABLE 2Intercorrelations (Pearson's *r*) between body fat variables in men (*n* = 437) and women (*n* = 655)¹

| | Visceral fat thickness (cm) ² | Subcutaneous abdominal fat thickness (cm) ² | BMI (kg/m ²) | Waist circumference (cm) | Total body fat (g) ³ |
|--|--|--|--------------------------|--------------------------|---------------------------------|
| Men | | | | | |
| Subcutaneous abdominal fat thickness (cm) ² | 0.22 | 1 | | | |
| BMI (kg/m ²) | 0.64 | 0.55 | 1 | | |
| Waist circumference (cm) | 0.66 | 0.60 | 0.72 | 1 | |
| Total body fat (g) ³ | 0.60 | 0.71 | 0.85 | 0.75 | 1 |
| Total abdominal fat (g) ³ | 0.70 | 0.62 | 0.72 | 0.71 | 0.92 |
| Women | | | | | |
| Subcutaneous abdominal fat thickness (cm) ² | 0.50 | 1 | | | |
| BMI (kg/m ²) | 0.68 | 0.64 | 1 | | |
| Waist circumference (cm) | 0.74 | 0.65 | 0.78 | 1 | |
| Total body fat (g) ³ | 0.69 | 0.74 | 0.82 | 0.75 | 1 |
| Total abdominal fat (g) ³ | 0.74 | 0.69 | 0.77 | 0.73 | 0.94 |

¹ All intercorrelations were significant (*P* < 0.001).² Measured by ultrasound.³ Measured by dual-energy X-ray absorptiometry; data were available for 297 men and 469 women.

postulation that the rate of weight gain from birth to adulthood, rather than low BW alone, alters visceral fat (27). This interpretation is also supported by our subsequent analysis of BMI as an effect modifier. When we stratified the analyses by BMI tertiles, the association between lower BW and higher visceral fat was indeed confined to those in the highest adult-BMI tertile. The group with the highest visceral fat was that with the combination of low BW and high adult BMI. Therefore, we suggest that it is the transition from low BW to high adult BMI, or simply the degree of weight gain between birth and adulthood, that leads to specifically greater visceral fat and related disease risks.

Many studies have identified rapid weight gain during infancy and childhood as a significant predictor of subsequent lean and fat masses (8, 31, 32). Demerath et al (20) showed that infant weight gain, but not BW, was positively related to visceral and subcutaneous abdominal fat assessed by MRI in 233 adults aged between 18–75 y old. That study supports our finding that rapid postnatal growth may be more important than the fetal environment for the programming of later body composition. However, unlike our study, Demerath et al (20) did not observe any differential effects on abdominal fat depots.

The mechanisms underlying these observations are not fully understood. It might be that the rapid weight gain and concurrent accumulation of central fat poses greater demands on organ function (29) that results in an unfavorable metabolic profile such as insulin resistance and elevated blood pressure. The thrifty phenotype hypothesis postulates that the fetus adapts to poor nutrition by selecting an appropriate growth trajectory in response to environmental cues in the presence of maternal malnutrition (33). However, if food consumption drastically increases postnatally and during childhood and results in subsequent obesity, the adaptations made by the fetus are no longer useful and are inappropriate for their programming (27, 34). Postnatal factors, such as nutrition, may contribute to or modify these associations and, therefore, represent potential targets for prevention against excess gains in visceral and subcutaneous abdominal fat. However, because our study only had a single assessment of adiposity, we were unable to identify when these excess gains in fat compartments occurred. Longitudinal studies could potentially identify the timing of accumulation of visceral fat after low BW, and we suggest that ultrasonography represents the most feasible tool to achieve the

TABLE 3Associations between birth weight and adult adiposity without (model A) and with (model B) adjustment for adult BMI¹

| Body composition variables | Model A | | Model B | |
|----------------------------|--------------------|----------|----------------------|----------|
| | <i>B</i> (95% CI) | <i>P</i> | <i>B</i> (95% CI) | <i>P</i> |
| BMI | 0.18 (0.07, 0.3) | 0.002 | — | — |
| Total body fat | 0.08 (−0.04, 0.2) | 0.3 | NA ² | — |
| Total abdominal fat | 0.02 (−0.1, 0.3) | 0.8 | −0.09 (−0.13, −0.07) | 0.002 |
| Visceral fat | 0.06 (−0.06, 0.2) | 0.3 | −0.07 (−0.15, −0.01) | 0.01 |
| Subcutaneous abdominal fat | 0.07 (−0.06, 0.1) | 0.4 | −0.01 (−0.11, 0.08) | 0.3 |
| Waist circumference | 0.03 (−0.01, 0.07) | 0.2 | −0.01 (−0.07, 0.03) | 0.4 |

¹ NA, not applicable. Results are shown from individual regression models for each variable adjusted for age, sex, educational level, and smoking status without (model A) or with (model B) BMI. *B* = partial regression coefficient (SD/1-kg change in birth weight).² Invalidated because of collinearity between BMI and total body fat.

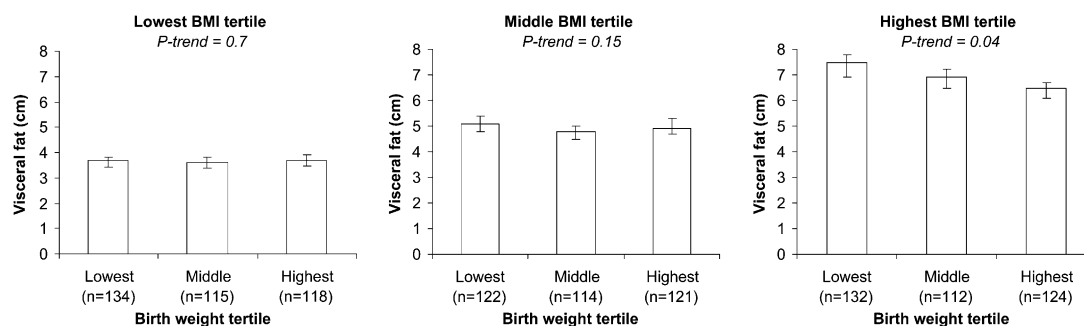


FIGURE 1. Mean (and 95% CI) visceral fat thickness according to birth weight tertile and stratified by adult BMI tertile.

necessary repeated measures of specific body fat compartments. Ultrasonography has been shown to provide valid estimates of abdominal adiposity; correlations between visceral fat thickness and visceral adipose tissue measured by reference imaging techniques range from 0.75 to 0.82 (21, 23, 35–38), and correlations between subcutaneous abdominal fat thickness and subcutaneous abdominal adipose tissue range from 0.63 to 0.74 (21, 38). Furthermore, in our study, the intra- and interobserver errors yielded a high degree of precision, which suggests that the ultrasound measures of visceral and subcutaneous fat thickness are reliable and reproducible.

A limitation of this study is that BW was self-reported. However, findings from other studies have shown that recalled BW is valid and reproducible and showed correlations between 0.6 and 0.8 with recorded BW (39–43). Only 73% of the sample reported their BW; however, there were no differences in body composition variables between those who reported BW and those who did not report BW (data not shown). Random error in the assessment of BW might have produced some underestimation of the strength of the associations. Previous studies reported that a 1-SD increase in visceral fat was associated with a 3–4-fold increase in metabolic syndrome risk (44). Therefore, the 0.07-SD rise in visceral fat per 1-kg lower BW that we observed might be expected to lead to an 8–10% increased risk of metabolic syndrome, without any correction for regression dilution. Gestational age was also not available in this cohort, and this could potentially confound the associations between BW and obesity-related variables. However, in other studies, adjustment for gestational age had little effect on associations with BW (45–48). We did not observe any associations between BW and waist circumference; other studies reported either positive associations between BW and waist circumference (49) or U-shaped relations (8, 17, 19). Waist circumference is notoriously difficult to measure because the anatomic landmarks can be hard to identify, particularly in larger individuals, and it is highly observer dependent.

In conclusion, we observed that BW was inversely associated specifically with visceral fat rather than subcutaneous abdominal fat in adults and only after adjustment for adult BMI. The dependency of this association on the adjustment for BMI may be interpreted as support for the hypothesis that rapid postnatal weight gain, rather than lower BW alone, promotes the accumulation of visceral fat. Further longitudinal studies are required to identify the specific timing of the increase in visceral fat and the postnatal factors that potentially modify this association.

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The authors' responsibilities were as follows—EDLR: performed data collection, statistical analysis, and manuscript preparation; KKO and RPS: provided guidance of EDLR's responsibilities; CD: provided critical input on the data analysis; NJW, SJG, NGF, UE, and RJFL (principal investigators of the Fenland Study): conceived the idea of the Fenland study and were responsible for the overall design and management of the study and the overall supervision of data collection; and all authors: provided interpretation of the results, revised the different versions of the manuscript, and approved the final version. None of the authors reported potential conflicts of interest.

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